(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 June 2002 (27.06.2002)

PCT

(10) International Publication Number
WO 02/50057 A1

(51) International Patent Classification[7]: C07D 401/10, 403/10, A61K 31/4184, 31/454, 31/496, 31/55, 31/551, A61P 21/02, 23/00, 25/08, 25/20, 25/22, 25/28

(21) International Application Number: PCT/DK01/00823

(22) International Filing Date:
12 December 2001 (12.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2000 01914 20 December 2000 (20.12.2000) DK

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

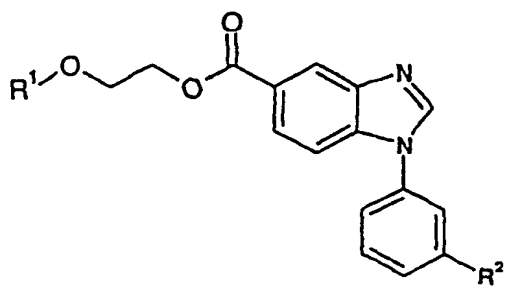
— *of inventorship (Rule 4.17(iv)) for US only*

Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL BENZIMIDAZOLE DERIVATIVES FOR THE TREATMENT OF GABA-ALFA MEDIATED DISORDERS



(I)

(57) Abstract: Novel benzimidazole derivatives of the general formula (I) where the meanings of R^1 and R^2 are as given in the claims and the description, pharmaceutical compositions containing these compounds, and methods of treatment therewith. The compounds are useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the $GABA_A$ receptor complex, and in particular for inducing and maintaining anaesthesia, sedation and muscle relaxation, as well as for combating febrile convulsions in children. The compounds of the invention may also be used by veterinarians.

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NOVEL BENZIMIDAZOLE DERIVATIVES FOR THE TREATMENT OF GABA-ALFA MEDIATED DISORDERS

TECHNICAL FIELD

The present invention relates to novel benzimidazole derivatives, pharmaceutical compositions containing these compounds, and methods of treatment therewith.

The compounds of the invention are useful in the treatment of central nervous system diseases and disorders, which are responsive to modulation of the $GABA_A$ receptor complex, and in particular for inducing and maintaining anaesthesia, sedation and muscle relaxation, as well as for combating febrile convulsions in children.

The compounds of the invention may also be used by veterinarians.

BACKGROUND ART

Agents that bind or interact with the modulatory sites on the $GABA_A$ receptor complex, such as for example the benzodiazepine receptor, can have either enhancing effect on the action of GABA, i.e. a positive modulatory effect of the receptor (agonists, partial agonists), an attenuating effect on the action of GABA, i.e. negative modulation of the receptor (inverse agonists, partial inverse agonists), or they can block the effect of both agonists and inverse agonists (antagonists or ligands without intrinsic activity).

Agonists generally produce muscle relaxant, hypnotic, sedative, anxiolytic, and/or anticonvulsant effects, while inverse agonists produce pro-convulsive, anti-inebriant or anxiogenic effects. Compounds with anxiolytic effects, but with or without reduced muscle relaxant, hypnotic and sedative effects, are characterised as partial agonists. Partial inverse agonists are considered to be useful as cognition enhancers.

Full agonists of the benzodiazepine receptor are considered useful as anaesthetics. However, many drugs presently available as anaesthetics, and especially pre-anaesthetics, give rise to hang-over effects as well as long awakening times, wherein careful monitoring of the patient is necessary. Anaesthetics with a long half-life may also impose difficulties during incidents of overdosing i.e. prolonged respiratory depression. Furthermore, some currently used drugs cannot be used for anaesthetising children as deaths have been reported in children after prolonged use of Propofol. Some anaesthetics are gasses, which inherently possesses a contamination problem for the medical staff.

A well known anaesthetic, Propofol, is administered as a mixture of soybean oil, glycerol and purified egg phosphatide, which mixture nourish bacterial growth. Administration of bacterially contaminated Propofol has been reported to cause sepsis and death [*Wiklund et al.*; The New England Journal of Medicine 1997 **337** (16) 1132-1141]. Further, compounds with a long *in vivo* half-life will give problems with

accumulation during and after prolonged treatment e.g. when administered to patients constrained to a respirator. Short half-lives wherein the compounds are metabolised to inactive metabolites allow for a predictable correlation of dose and duration of pharmacological effect.

Ideally the anaesthestising effect should be observed shortly after a bolus injection or infusion of the compound. A rapid onset of action minimises the period of anxiety and uneasiness experienced by patients going into surgery.

Patients suffering from severe and continuous epileptic attacks presently treated with large amounts of sedatives, e.g. benzodiazepines, will benefit from shorter acting compounds with no hang-over or long lasting sedating effect.

As the preferred route of administration is by intravenous injection or infusion, the anaesthestising compounds should preferably be water soluble.

EP 616807 describes benzimidazole compounds for use as benzodiazepine receptor ligands.

WO 96/33194, WO 96/33191 and WO 96/33192 describe benzimidazole compounds having affinity for the GABA receptor complex.

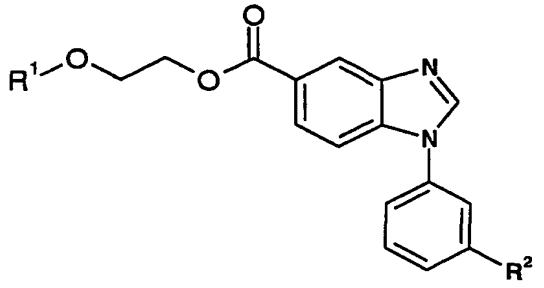
WO 98/34923 describes phenylbenzimidazole derivatives as ligands for the GABA receptor complex.

WO 98/17651 describes benzimidazole compounds for use as e.g. anaesthetics. However, the presently disclosed compounds are superior to the compounds previously described.

SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds useful as anaesthetics and/or pre-anaesthetics, sedatives, muscle relaxants, and for the treatment of febrile convulsions in children, status epilepticus, for use to patients constrained to a respirator as well as for veterinarian uses. A further object of the invention is to produce compounds which show a rapid onset of action. A still further object of the invention is to produce compounds with less hang-over effect and/or less long lasting sedation effect thereby showing a faster recovery of the patients.

In its first aspect, the invention provides a benzimidazole derivative represented by the general Formula I,



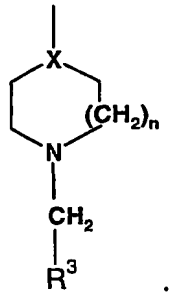
(I)

or a pharmaceutically acceptable salt thereof,

wherein

R^1 represents hydrogen or methyl;

R^2 represents



;

wherein

X represents N or CH;

n is 1 or 2;

R^3 represents $-CO_2R^4$ or $-CO\text{-}NR^4R^5$;

wherein R^4 represents methyl or ethyl; and

R^5 represents methyl or ethyl;

with the proviso that the compound is not

2-Methoxyethyl 1-(3-(4-(ethoxycarbonylmethyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-(methoxycarbonylmethyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-(ethoxycarbonylmethyl)piperazin-1-yl)phenyl)benzimidazole-5-carboxylate;

2-Methoxyethyl 1-(3-(4-(methoxycarbonylmethyl)piperazin-1-yl)phenyl)benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate; or

2-Methoxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate.

In its second aspect, the invention provides a pharmaceutical composition containing a therapeutically effective amount of a benzimidazole derivative according to the invention, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In its third aspect, the invention provides a use of a benzimidazole derivative according to the invention for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex.

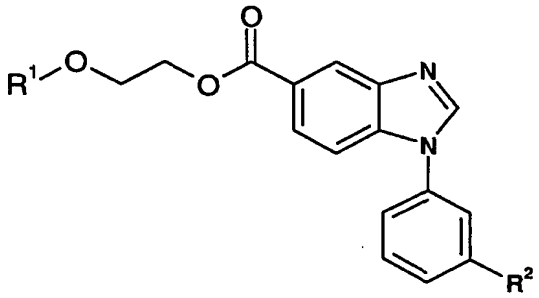
In its fourth aspect, the invention provides a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the GABA receptor complex, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a benzimidazole derivative according to the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and the working examples.

DETAILED DISCLOSURE OF THE INVENTION

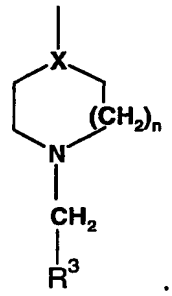
Benzimidazole Derivatives

In its first aspect the invention provides novel benzimidazole derivatives. The benzimidazole derivatives of the invention are represented by the general Formula I,



(I)

or a pharmaceutically acceptable salt thereof,
wherein
R^1 represents hydrogen or methyl;
R^2 represents



;

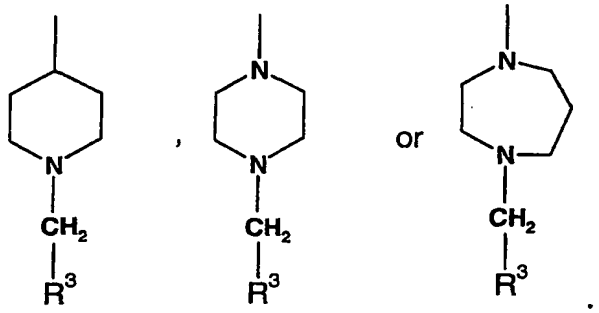
wherein
X represents N or CH;
n is 1 or 2;
R^3 represents $-CO_2R^4$ or $-CO\text{-}NR^4R^5$;

wherein R^4 represents methyl or ethyl; and
R^5 represents methyl or ethyl;
with the proviso that the compound is not
2-Methoxyethyl 1-(3-(4-(ethoxycarbonylmethyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(4-(methoxycarbonylmethyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(4-(ethoxycarbonylmethyl)piperazin-1-yl)phenyl)benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-(methoxycarbonylmethyl)piperazin-1-yl)phenyl)benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate; or
2-Methoxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)-piperazin-1-yl)-phenyl)-benzimidazole-5-carboxylate.

In one embodiment, R^1 represents hydrogen. In a second embodiment, R^1 represents methyl.

In a further embodiment, X represents N. In a still further embodiment, X represents CH. In a further embodiment, n is 1. In a still further embodiment, n is 2.

In a special embodiment, R^2 represents



;

wherein R^3 is defined as above.

In a still further embodiment, R^3 represents $-CO_2R^4$. In a further embodiment, R^3 represents $-CO\text{-}NR^4R^5$. In a further embodiment, R^4 represents methyl. In a still further embodiment, R^4 represents ethyl. In a further embodiment, R^5 represents methyl. In a still further embodiment, R^5 represents ethyl.

In a special embodiment, R^2 represents
1-(ethoxycarbonylmethyl)piperidin-4-yl or
1-(methoxycarbonylmethyl)piperidin-4-yl.

In a further special embodiment, R^2 represents
4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl;
1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl;

4-((N,N-dimethylcarbamoyl)methyl)-homopiperazin-1-yl; or
4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl.

In a more special embodiment, the benzimidazole derivative is
2-Hydroxyethyl 1-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenyl)benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
or a pharmaceutically acceptable salt thereof.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the

maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with a pharmaceutically acceptable solvents such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Prodrugs

The chemical compound of the invention may be administered as such or in the form of a suitable prodrug.

The term "prodrug" denotes a compound, which is a drug precursor and which, following administration and absorption, release the drug in vivo via some metabolic process.

Particularly favoured prodrugs are those that increase the bioavailability of the compounds of the invention (e.g. by allowing an orally administrered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a specific biological compartment (e.g. the brain or lymphatic system).

Thus examples of suitable prodrugs of the substances according to the invention include compounds modified at one or more reactive or derivatizable groups of the parent compound. Of particular interest are compounds modified at a carboxyl

group, a hydroxyl group, or an amino group. Examples of suitable derivatives are esters or amides.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

The benzimidazole derivatives of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either

a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily

or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated and the route of administration, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently

contemplated that pharmaceutical compositions containing of from about 0.01 to about 500 mg of active ingredient per individual dose, preferably of from about 0.1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.01 µg/kg i.v. and 0.1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Biological Activity

It is an object of the present invention to provide compounds capable of modulating the $GABA_A$ receptor complex, which object is met by the provision of the novel benzimidazole derivatives of Formula I.

The benzimidazole derivatives of the invention are particularly useful as anaesthetics and/or pre-anaesthetics, for inducing and maintaining anaesthesia, as sedatives, as muscle relaxants, and for combating febrile convulsions in children, status epilepticus, for use to patients constrained to a respirator.

The benzimidazole derivatives of the invention show a short duration of action, they are water soluble at therapeutic relevant doses, and are particular well suited for intravenous administration.

The compounds of the invention may also be used by veterinarians.

The benzimidazole derivatives of the invention show high to moderate affinity for the benzodiazepine receptor as measured by displacement at ^{3}H-flunitrazepam *in vitro* as well as *in vivo*. The most preferred compounds are full agonists i.e. they exert a high maximal effect in the seizure test as described in the application.

Preferred compounds are full agonists on the $GABA_A$ receptor complex, e.g. as measured by the anticonvulsant activity in the ptz-test described in Example 8. The most preferred compounds are those which increase the tolerated dose the most.

The benzimidazole derivatives of the invention show half-lives of below 30 minutes, which allows for a short duration of action. Preferred half-lives are in the range of from about 30 seconds to about 20 minutes. Most preferred half-lives are in the range of from about 2 to about 5 minutes.

The preferred compounds induce a rapid onset of anaesthesia, i.e. in less than 1-2 minutes. Most preferred is an onset of anaesthesia in less than 1 minute.

Awakening from anaesthesia following a bolus injection (i.v.), or following the attenuation of an infusion, should occur within a short period of time, i.e. of from about 5 to about 30 minutes, preferably of from about 5 to about 10 minutes, after which time

the patient should normalise rapidly, i.e. in less than 40 minutes, preferably in less than 20 minutes, as measured from awakening.

The compounds of this invention can be used together with analgetic compounds such as Remifentanile, Fentanyl, or other opiods.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of benzimidazole derivative of the invention.

In a more preferred embodiment the invention provides a method for the induction or maintenance of anaesthesia or pre-anaesthesia, muscle relaxation or sedation, or for the treatment, prevention or alleviation of fewer cramps or status epilepticus.

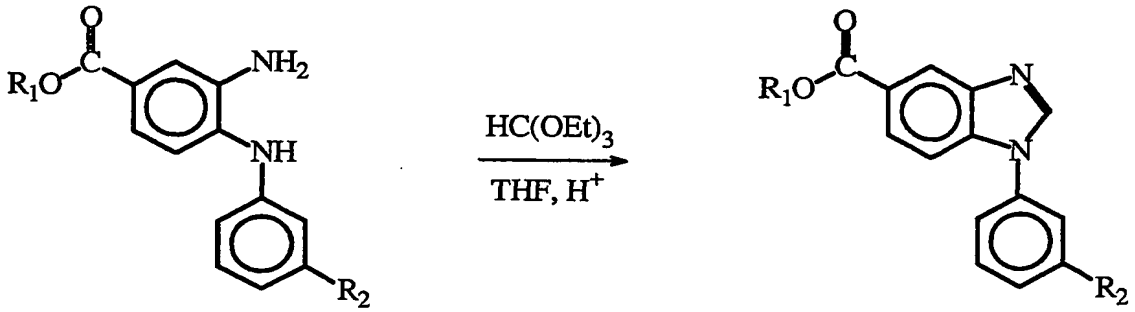
It is at present contemplated that suitable infusion rates are in the range of from about 0.01 to about 100 mg/kg/hour, more preferred of from about 0.1 to about 15 mg/kg/hour, dependent upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Any possible combination of two or more of the embodiments described herein is comprised within the scope of the present invention.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

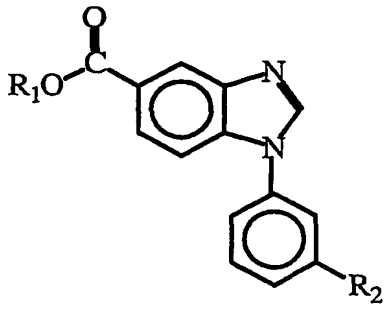
Example 1

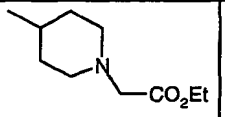
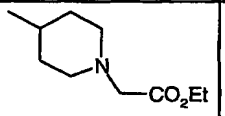
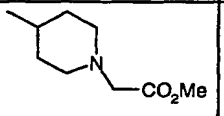
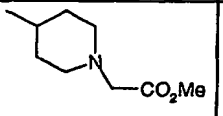
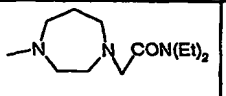
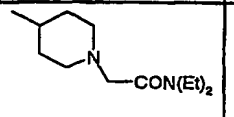
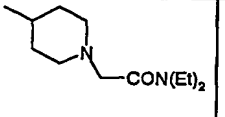


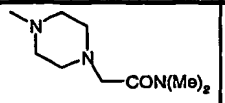
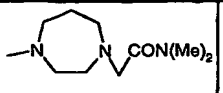
2 1

The benzimidazoles of Table 1 were all prepared according to the above scheme as exemplified for compound **1a**, below.

Table 1



Comp. No.	R_1	R_2	Mp (°C)	Yield (%)	Starting material	Salt
1a	$HO(CH_2)_2$		Un-defined	58	**2a**	HCl
1b	$MeO(CH_2)_2$		Un-defined	77	**2b**	HCl
1c	$HO(CH_2)_2$		123-158	25	**2c**	HCl
1d	$MeO(CH_2)_2$		60-74	39	**2d**	HCl
1e	$MeO(CH_2)_2$		80-84	47	**2e**	HCl
1f	$HO(CH_2)_2$		Un-defined	43	**2f**	HCl
1g	$MeO(CH_2)_2$		112-130	68	**2g**	HCl

Comp No.	R_1	R_2	Mp (°C)	Yield (%)	Starting material	Salt
1h	$MeO(CH_2)_2$		Un-defined	43	2h	HCl
1i	$MeO(CH_2)_2$		84-86	80	2i	HCl

2-Hydroxyethyl 1-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenyl)benzimidazole-5-carboxylate (**1a**): A mixture of **2a** (2.35 g; 5.33 mmol), triethylorthoformate (1.4 ml; 8 mmol) and a catalytic amount of p-toluenesulfonic acid in tetrahydrofurane (20 ml) was heated to reflux for 60 min. The cooled mixture was diluted with ethyl acetate and washed with aqueous sodium hydroxide (1 M). The organic phase was dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using ethyl acetate as the eluent. The product was precipitated as the hydrochloride by addition of etheral hydrogen chloride to the eluate. Yield: 1.5 g (58%). The following compounds were prepared in analogy with Compound **1a**:

2-Methoxyethyl 1-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate (**1b**) from **2b**.

2-Hydroxyethyl 1-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate (**1c**) from **2c**. Mp. 123-158°C. A mixture of methanol and ethyl acetate (1:9 v/v) was used as the eluent for the column chromatographic purification.

2-Methoxyethyl 1-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate (**1d**) from **2d**. Mp. 60-74°C.

2-Methoxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl)phenyl)-benzimidazole-5-carboxylate (**1e**) from **2e**. Mp. 80-84°C. A mixture of 2-propanol and ethyl acetate (3:7 v/v) was used as the eluent.

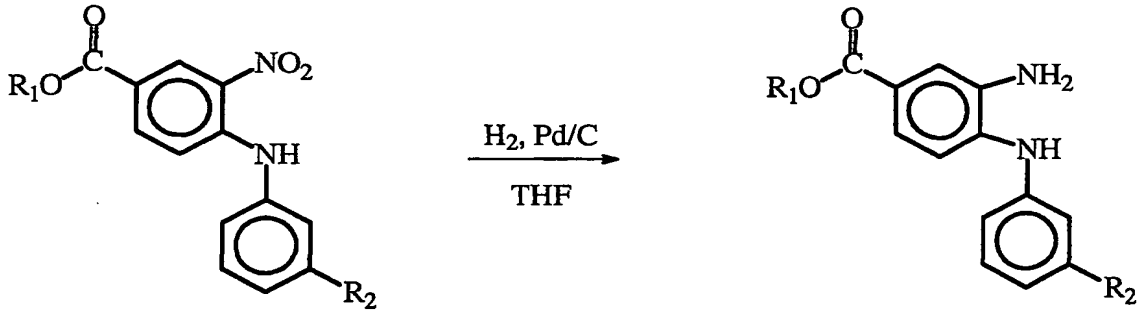
2-Hydroxyethyl 1-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate (**1f**) from **2f**. A mixture of methanol and ethyl acetate (1:5 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate (**1g**) from **2g**. Mp. 112-130°C. A mixture of methanol and ethyl acetate (1:9 v/v) was used as the eluent.

2-Methoxyethyl 1-(3-(4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate (**1h**) from **2h**. A mixture of methanol and ethyl acetate (1:5 v/v) was used as the eluent for the column-chromatographic purification.

2-Methoxyethyl 1-(3-(4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl)phenyl)-benzimidazole-5-carboxylate (**1i**) from **2i**. Mp. 84-86°C. A mixture of methanol and ethyl acetate (3:7 v/v) was used as the eluent.

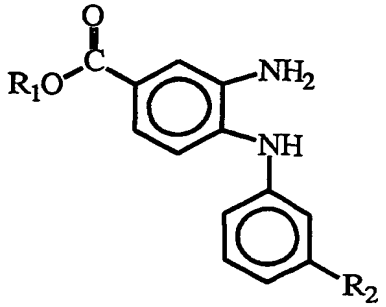
Example 2

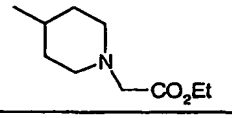
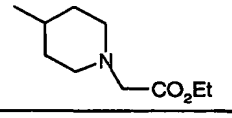
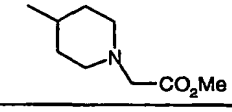
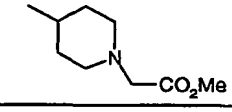
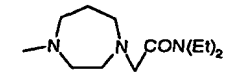
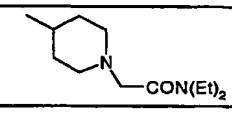
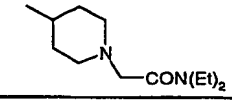
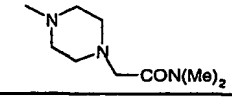
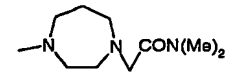


3 2

The diamines of Table 2 were all prepared quantitatively by hydrogenation of the corresponding nitroanilines (**3**), according to the above scheme as exemplified for **2a** below.

Table 2



Compound No.	R_1	R_2	Starting material
2a	$HO(CH_2)_2$		3a
2b	$MeO(CH_2)_2$		3b
2c	$HO(CH_2)_2$		3c
2d	$MeO(CH_2)_2$		3d
2e	$MeO(CH_2)_2$		3e
2f	$HO(CH_2)_2$		3f
2g	$MeO(CH_2)_2$		3g
2h	$MeO(CH_2)_2$		3h
2i	$MeO(CH_2)_2$		3i

2-Hydroxyethyl 3-amino-4-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)-phenylamino)-benzoate (**2a**). **3a** (2.8 g; 5.94 mmol) was suspended in tetrahydrofurane. Palladium catalyst (50 mg, 5% on activated carbon) was added and the mixture was hydrogenated at ambient pressure until the hydrogen uptake had ceased. The mixture was filtered through celite and the filtrate was evaporated to dryness to leave **2a**, quantitatively.

The following compounds were prepared in analogy with Compound **2a**:

2-Methoxyethyl 3-amino-4-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)-phenylamino)-benzoate (**2b**) from **3b**.

2-Hydroxyethyl 3-amino-4-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)-phenylamino)-benzoate (**2c**) from **3c**.

2-Methoxyethyl 3-amino-4-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)-phenylamino)-benzoate (**2d**) from **3d**.

2-Methoxyethyl 3-amino-4-(3-(4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl)-phenylamino)-benzoate (**2e**) from **3e**.

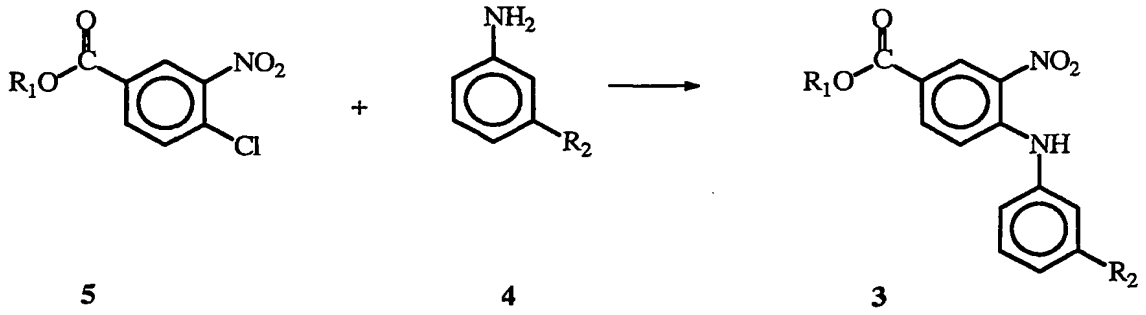
2-Hydroxyethyl 3-amino-4-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)-phenylamino)-benzoate (**2f**) from **3f**.

2-Methoxyethyl 3-amino-4-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)-phenylamino)-benzoate (**2g**) from **3g**.

2-Methoxyethyl 3-amino-4-(3-(4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl)-phenylamino)-benzoate (**2h**) from **3h**.

2-Methoxyethyl 3-amino-4-(3-(4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl)-phenylamino)-benzoate (**2i**) from **3i**.

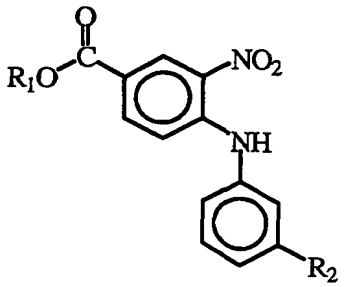
Example 3

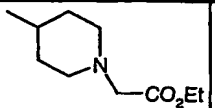
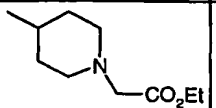
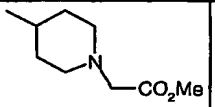
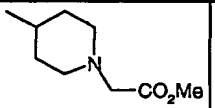
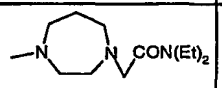
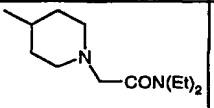
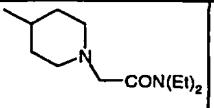
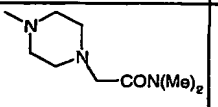
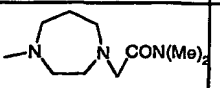


5 4 3

The nitroanilines of Table 3 were prepared by reaction of 4-chloro-3-nitrobenzoates **5** with substituted anilines (**4**), according to the above scheme as exemplified for compound **3a** below.

Table 3



Comp. No.	R_1	R_2	Starting materials	Yield (%)
3a	$HO(CH_2)_2$		**4a, 5b**	62
3b	$MeO(CH_2)_2$		**4a, 5a**	65
3c	$HO(CH_2)_2$		**4b, 5b**	60
3d	$MeO(CH_2)_2$		**4b, 5a**	76
3e	$MeO(CH_2)_2$		**4c, 5a**	91
3f	$HO(CH_2)_2$		**4d, 5b**	44
3g	$MeO(CH_2)_2$		**4d, 5a**	53
3h	$MeO(CH_2)_2$		**4e, 5a**	100
3i	$MeO(CH_2)_2$		**4f, 5a**	62

2-Hydroxyethyl 3-nitro-4-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenylamino)-benzoate **3a**. A mixture of **5b** (2.3 g; 9.54 mmol), **4a** (2.5 g; 9.54 mmol) and triethylamine (1.3 ml; 9.54 mmol) in NMP (10 ml) was heated to 100°C overnight. The cooled mixture was partitioned between water and ethyl acetate. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel using a mixture of ethyl acetate and ligroin (1:1 v/v) as the eluent. Yield: 2.8 g (62%).

The following compound were prepared in analogy with Compound **3a**:

2-Methoxyethyl 3-nitro-4-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenylamino)-benzoate (**3b**) from **4a and 5a**.

2-Hydroxyethyl 3-nitro-4-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenylamino)-benzoate (**3c**) from **4b and 5b**.

2-Methoxyethyl 3-nitro-4-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)-phenylamino)-benzoate (**3d**) from **4b and 5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl)-phenylamino)-benzoate (**3e**) from **4c and 5a**.

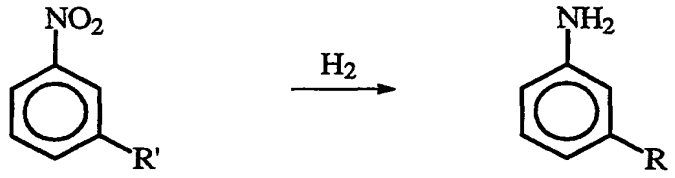
2-Hydroxyethyl 3-nitro-4-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)-phenylamino)-benzoate (**3f**) from **4d and 5b**.

2-Methoxyethyl 3-nitro-4-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)-phenylamino)-benzoate (**3g**) from **4d and 5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl)-phenylamino)-benzoate (**3h**) from **4e and 5a**.

2-Methoxyethyl 3-nitro-4-(3-(4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl)-phenylamino)-benzoate (**3i**) from **4f and 5a**.

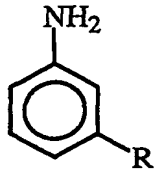
Example 4

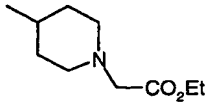
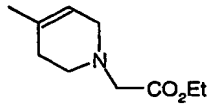
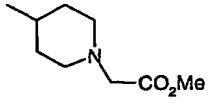
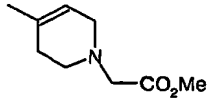
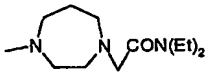
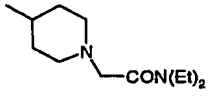
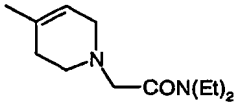
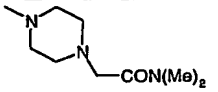
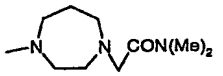


6 **4**

The substituted anilines of Table 4 were prepared by hydrogenation of the corresponding nitro compounds (**6**) as exemplified by compound **4a** below.

Table 4



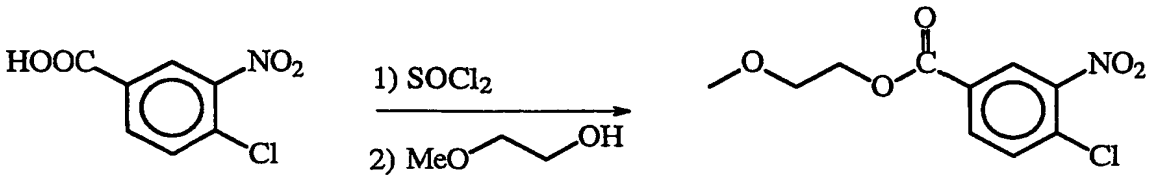
Comp. No.	R	Starting material	R'	Preparation of starting material
4a		**6a**		Example 6a
4b		**6b**		Example 6b
4c		**6c**	R	Example 6c
4d		**6d**		Example 6d
4e		**6e**	R	Example 6e
4f		**6f**	R	Example 6f

Ethyl 2-(4-(3-aminophenyl)piperidin-1-yl)acetate **4a**. To a solution of **6a** (6.0g; 19.9 mmol) in abs. ethanol (50 ml) was added palladium catalyst (1.5g, 5% Pd on activated carbon) and the mixture was hydrogenated at ambient pressure until the hydrogen uptake had ceased. Filtration through celite and evaporation of solvent left **4a**, quantitatively.

The following compound were prepared in analogy with Compound **4a**:

Methyl 2-(4-(3-aminophenyl)piperidin-1-yl)acetate (**4b**) from **6b.**
3-(4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl)aniline (**4c**) from **6c.**
3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)aniline (**4d**) from **6d.**
3-(4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl)aniline (**4e**) from **6e.**
3-(4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl)aniline (**4f**) from **6f.**

Example 5



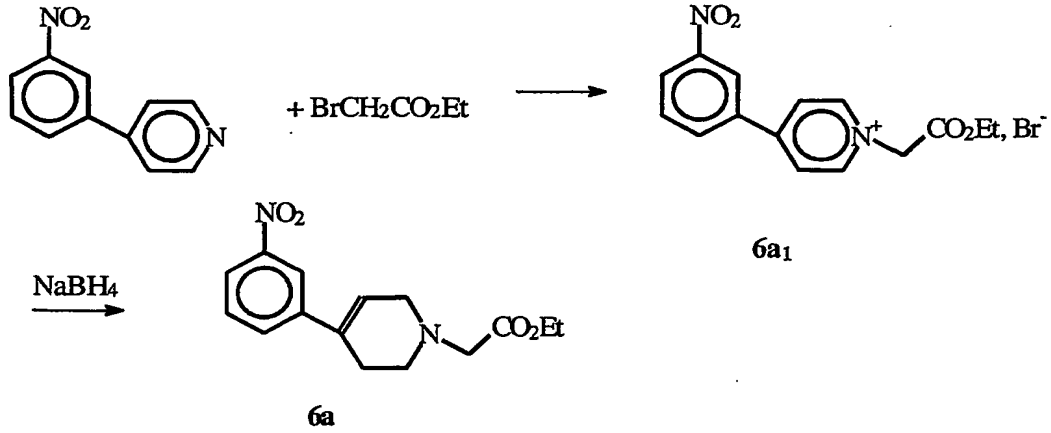
2-Methoxyethyl 4-chloro-3-nitrobenzoate **5a**. A mixture of 4-chloro-3-nitrobenzoic acid (10.0 g; 49.6 mmol) and thionylchloride (50 ml) was heated to reflux overnight. The excess of thionylchloride was removed by evaporation and 2-methoxyethanol (50 ml) was added. The resulting mixture was stirred at 80°C for 4 hours. The cooled solution was diluted with water (500 ml) and extracted with ethyl acetate (2 × 100 ml). The organic extract was dried over magnesium sulphate and concentrated under reduced pressure. Trituration of the residue with petroleum ether left **5a** (8.0 g; 62%) as a low melting solid (Mp. 33-35°C).

The following compound were prepared in analogy with Compound **5a**:

2-Hydroxyethyl 4-chloro-3-nitrobenzoate (**5b**).

Example 6a

1-(Ethoxycarbonylmethyl)-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6a**).



1-(Ethoxy-carbonyl-methyl)-4-(3-nitrophenyl)-pyridinium bromide (**6a$_1$**). A mixture of 4-(3-nitrophenyl)pyridine (2.25 g; 11.3 mmol) and ethyl 2-bromoacetate (1.5 ml; 13.5 mmol) in THF (10 ml) was heated to reflux overnight. The cooled mixture was filtered and the crystalline product was washed with THF and dried to leave **6a$_1$** (3.49 g; 84%).

1-(Ethoxy-carbonyl-methyl)-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6a**). To a suspension of **6a**$_1$ (2.90 g; 7.88 mmol) in abs. ethanol (50 ml) was added sodium borohydride (0.60 g; 15.9 mmol) in portions over 1 hour. The mixture was stirred at ambient temperature for two days, poured into ice-water and extracted with ethyl acetate. The extract was dried over sodium sulphate, concentrated and eluted through silica gel with ethyl acetate to yield **6a** (1.65 g; 72%).

Example 6b

1-(Methoxycarbonylmethyl)-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6b**).

Prepared in analogy with example 6a using methyl 2-bromoacetate as the alkylating agent.

Example 6c

1-((N,N-diethylcarbamoyl)methyl)-4-(3-nitrophenyl)-homopiperazine (**6c**).

6c was prepared in analogy with example 6e using homopiperazine instead of piperazine and 2-chloro-N,N-diethylacetamide as the alkylating agent.

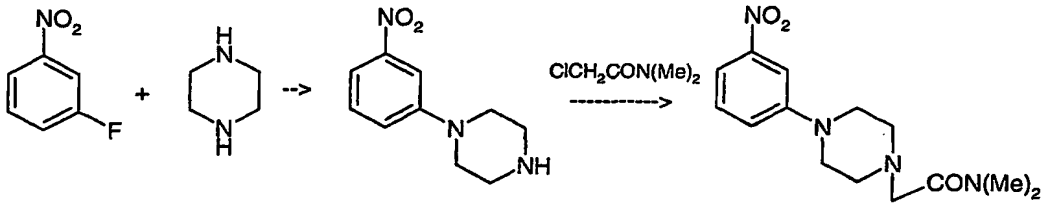
Example 6d

1-((N,N-diethylcarbamoyl)methyl)-4-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine (**6d**).

6d was prepared in analogy with example 6a using 2-chloro-N,N-diethylacetamide as the alkylating agent.

Example 6e

1-((N,N-dimethylcarbamoyl)methyl)-4-(3-nitrophenyl)piperazine (**6e**).



1-(3-Nitrophenyl)-piperazine (**6e**$_1$). A suspension of 3-fluoronitrobenzene (23 ml; 0.21 mol) and piperazine (55.5 g; 0.64 mol) in anhydrous NMP (30 ml) was heated to 70°C for five days. The cooled mixture was diluted with water (250 ml) and extracted with dichloromethane. The combined extracts were dried over magnesium sulphate and concentrated under reduced pressure. The residue was purified by column-chromatography on silica gel eluting subsequently with mixtures of ethyl acetate and methanol (4:1 v/v) and (1:1 v/v) to leave the desired product as oily crystals (30.7 g; 71%).

To a solution of 1-(3-nitrophenyl)-piperazine (**6e$_1$**) (10.0 g; 41.2 mmol) in DMF (50 ml) was added triethylamine (6 ml; 43.2 mmol), potassium iodide (0.3 g) and 2-chloro-N,N-dimethylacetamide (4.5 ml; 41.2 mmol). The mixture was stirred at 100°C for 30 min and left at ambient temperature overnight. The reaction mixture was poured into ice-water (200 ml) and the precipitate was filtered off, washed with water and dried to leave 9.8 g (81 %) of **6e**.

Example 6f

1-((N,N-dimethylcarbamoyl)methyl)-4-(3-nitrophenyl)-homopiperazine (**6f**).

6f was prepared in analogy with example 6c using 2-chloro-N,N-dimethylacetamide as the alkylating agent.

Example 7

***In vitro* and *in vivo* Binding Activity**

The GABA recognition site and the benzodiazepine modulatory unit can selectively be labelled with ^{3}H-muscimol and ^{3}H-flunitrazepam, respectively.

7A: *In vitro* inhibition of ^{3}H-flunitrazepam (^{3}H-FNM) binding

Tissue Preparation

Preparations are performed at 0-4°C unless otherwise indicated. Cerebral cortex from male Wistar rats (150-200 g) is homogenised for 5-10 sec in 20 ml Tris-HCl (30 mM, pH 7.4) using an Ultra-Turrax homogeniser. The suspension is centrifuged at 27,000 x g for 15 min and the pellet is washed three times with buffer (centrifuged at 27,000 x g for 10 min). The washed pellet is homogenized in 20 ml of buffer and incubated on a water bath (37°C) for 30 min to remove endogenous GABA and then centrifuged for 10 min at 27,000 x g. The pellet is then homogenized in buffer and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 30 ml buffer and the preparation is frozen and stored at -20°C.

Assay

The membrane preparation is thawed and centrifuged at 2°C for 10 min at 27,000 x g. The pellet is washed twice with 20 ml 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogeniser and centrifuged for 10 min at 27,000 x g. The final pellet is resuspended in 50 mM Tris-citrate, pH 7.1 (500 ml buffer per g of original tissue), and then used for binding assays. Aliquots of 0.5 ml tissue are added to 25 µl of test solution and 25 µl of ^{3}H-FNM (1 nM, final concentration), mixed and incubated for 40 min at 2°C. Non-specific binding is determined using Clonazepam (1 µM, final concentration). After incubation the samples are added 5 ml of ice-cold buffer and poured directly onto

Whatman GF/C glass fibre filters under suction and immediately washed with 5 ml ice-cold buffer. The amount of radioactivity on the filters is determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

Results

25-75% inhibition of specific binding must be obtained, before calculation of an IC_{50}. The test value will be given as IC_{50} (the concentration (µM) of the test substance which inhibits the specific binding of ^{3}H-FNM by 50%).

$$IC_{50} = (\text{applied test substance concentration, } \mu M) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where

C_o is specific binding in control assays, and

C_x is the specific binding in the test assay.

(The calculations assume normal mass-action kinetics).

7B: *In vivo* Inhibition of ^{3}H-FNM binding

Introduction

In vitro binding studies have demonstrated that the benzodiazepine [^{3}H]FNM binds selectively and with high-affinity to the $GABA_A$ receptor-ion channel complex. [^{3}H]FNM can also be used for *in vivo* receptor labelling studies in mouse. Accumulation of [^{3}H]FNM binding will occur all over the brain as $GABA_A$ receptors are widely distributed. The specific binding of [^{3}H]FNM can be partly or completely prevented by simultaneous or prior administration of pharmacologically active benzodiazepines or by some benzodiazepine-like compounds.

Method

All test substances used are solutions prepared in 10% TWEEN 80. Groups of three female NMRI mice (25 g) are injected i.v. via the tail vein with 5.0 µCi of [^{3}H]FNM in 0.2 ml saline. Fifteen min after injection with [^{3}H]FNM the test substance is administered i.v. Twenty min after injection with [^{3}H]FNM, mice are killed by decapitation, the forebrains rapidly excised and homogenized in 12 ml of ice-cold 50 mM Tris-citrate, pH 7.1 using an Ultra-Turrax homogenizer. Three aliquots of 1 ml are immediately filtered through GF/C glass fibre filters and washed with 2 × 5 ml of ice-cold buffer. The amounts of

radioactivity on the filters and in 200 µl of the homogenate are determined by conventional scintillation counting. Groups of untreated mice serves as controls. To determine non-specific binding groups of mice are injected with Clonazepam (25 mg/kg) i.p. 10 min before [^{3}H]FNM injection. Specific binding is the amount of binding in controls minus the amount of binding in Clonazepam treated mice.

Results

The ED_{50} value is determined from dose response curves. If only one dose of test substance is administered, the ED_{50} value is calculated as follows, provided that the inhibition of specific binding is within the range of 25-75%.

$$ED_{50} = (\text{administered dose, mg/kg}) \times \frac{1}{\left(\frac{C_o}{C_x} - 1\right)}$$

where C_o is specific binding in controls and C_x is the specific binding in mice treated with test substance.

Example 8

PTZ Clonic Convulsions

The purpose of this test is to show antagonism of clonic convulsions induced by pentylenetetrazol (PTZ). PTZ induces clonic convulsions in mice after i.v. infusion. Antagonism of PTZ-induced convulsions is a measure for the agonistic character of ligands for the benzodiazepine recognition site.

Procedure

Female NMRI mice (Bomholdtgaard, Ry), 20 g, 6 mice in each group are administered i.v. with vehicle or test substance. After five minutes the PTZ-solution is infused intravenously at a speed of 0.7 ml/minute through a cannula placed in the tail vein. The time from initiation of the infusion to appearance of clonic convulsions is recorded.

The dose of PTZ required for inducing convulsion in each mouse is calculated as PTZ/kg body weight. Means ±sd for each experimental group of 6 mice is calculated. ED_{100} is calculated by linear regression expressing the dose increasing the PTZ threshold to 100 mg PTZ/kg.

The threshold of vehicle treated controls is in the range of 37-39 mg PTZ/kg. As a control in each series of experiments PTZ is infused into 6 vehicle treated mice.

Example 9

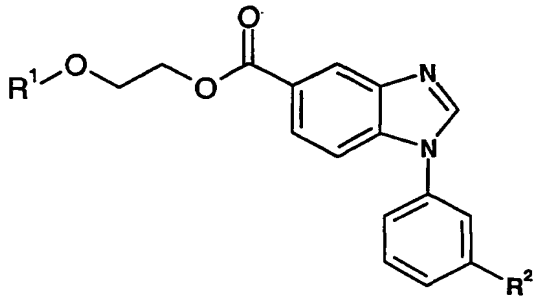
Evaluation of Efficacy

Selected compounds exhibiting a promising profile in the above tests may be evaluated with respect to efficacy and duration of action and compared to prior art as follows.

Aqueous solutions of the test substances (50 mg/ml isotonic glucose) were administered to pigs (25-30 kg) as bolus injections. The actual dose of each substance is included in the table below. The pigs were observed with respect to the time of induction of anaesthesia, the duration of anaesthesia and the normalising time following awakening from anaesthesia.

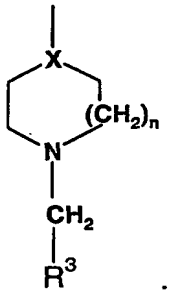
Claims:

1. A benzimidazole derivative represented by the general Formula I,



(I)

or a pharmaceutically acceptable salt thereof,
wherein
R^1 represents hydrogen or methyl;
R^2 represents



;

wherein
X represents N or CH;
n is 1 or 2;
R^3 represents $-CO_2R^4$ or $-CO\text{-}NR^4R^5$;
wherein R^4 represents methyl or ethyl; and
R^5 represents methyl or ethyl;

with the proviso that the compound is not
2-Methoxyethyl 1-(3-(4-(ethoxycarbonylmethyl)piperazin-1-yl)-phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(4-(methoxycarbonylmethyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(4-(ethoxycarbonylmethyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-(methoxycarbonylmethyl)piperazin-1-yl)phenyl)benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate; or
2-Methoxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)-piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate.

2. The benzimidazole derivative of claim 1, wherein
R^3 represents $-COR^4$;
wherein R^4 is as defined in claim 1.

3. The benzimidazole derivative of claims 1 or 2, wherein
R^2 represents
1-(ethoxycarbonylmethyl)-piperidin-4-yl or
1-(methoxycarbonylmethyl)-piperidin-4-yl.

4. The benzimidazole derivative of claim 1, wherein
R^3 represents $-CO-NR^4R^5$;
wherein R^4 and R^5 are as defined in claim 1.

5. The benzimidazole derivative of claims 1 or 4 wherein
R^2 represents
4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl;
1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl;
4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl; or
4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl.

6. The benzimidazole derivative of any one of the claims 1-3, which is
2-Hydroxyethyl 1-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(1-(ethoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Hydroxyethyl 1-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(1-(methoxycarbonylmethyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
or a pharmaceutically acceptable salt thereof.

7. The benzimidazole derivative of any one of the claims 1 and 4-5, which is
2-Methoxyethyl 1-(3-(4-((N,N-diethylcarbamoyl)methyl)homopiperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;

2-Hydroxyethyl 1-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(1-((N,N-diethylcarbamoyl)methyl)piperidin-4-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-((N,N-dimethylcarbamoyl)methyl)piperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
2-Methoxyethyl 1-(3-(4-((N,N-dimethylcarbamoyl)methyl)homopiperazin-1-yl)phenyl)-benzimidazole-5-carboxylate;
or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition containing a therapeutically effective amount of a benzimidazole derivative according to any one of claims 1-7, or a pharmaceutically acceptable addition salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

9. The use of a benzimidazole derivative according to any one of claims 1-7 for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the GABA receptor complex.

10. The use according to claim 9, wherein the medicament is for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fewer cramps or status epilepticus.

11. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to modulation of the GABA receptor complex, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a benzimidazole derivative according to any one of claims 1-7.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 01/00823

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/10 C07D403/10 A61K31/4184 A61K31/454 A61K31/496
A61K31/55 A61K31/551 A61P21/02 A61P23/00 A61P25/08
A61P25/20 A61P25/22 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, EMBASE, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
8 X	WO 98 17651 A (NEUROSEARCH AS) 30 April 1998 (1998-04-30) abstract page 2, line 4 - line 8 page 25, line 15 - line 24; examples; table 4 page 32 -page 33; claims compounds 4a-m	1-11
8 P,X	WO 00 78728 A (NEUROSEARCH AS) 28 December 2000 (2000-12-28) abstract page 1, line 18 - line 31 page 28, line 31 - line 37 page 30; example 1 page 30 -page 34; table 1 claims	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2002	28. 03. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Per Renström

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00823

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 11

Claim 11 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1 (iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 01/00823

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9817651 A	30-04-1998	AU 726447 B2	09-11-2000
		AU 4616197 A	15-05-1998
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		CZ 9901272 A3	15-09-1999
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		US 6218547 B1	17-04-2001
WO 0078728 A	28-12-2000	AU 5391000 A	09-01-2001
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